Remarks

Receipt is acknowledged of the Office Action dated February 12, 2003. In the Action, the Examiner has withdrawn claims 44-56 from consideration, pursuant to the Restriction Requirement. Of the elected claims, the Examiner has rejected claims 34-43 as indefinite. The Examiner has also rejected claims 34-43 as lacking enablement. The Examiner has also rejected claims 34 and 59 as anticipated. The Examiner has also rejected claims 34-43 and 57-59 as obvious.

Applicants have canceled claims 35, 44-56, 58 and 59, amended claims 34, 38, 39, 41-43, and 57, and added claim 60. Consequently, claims 34, 36, 37-43, 57 and 60 will be pending with entry of the amendments. Support for the amendments is found throughout the originally-filed specification and claims, for example, page 17, lines 10-15, describing between 2-12 UDP-sugar molecules, and page 5, lines 35-38, describing concentrations of hyaluronic acid fragments. Reconsideration and withdrawal of any outstanding objections and rejections in view of the amendments and remarks set forth below are respectfully requested.

Rejections under 35 U.S.C.§ 112, second paragraph

In paragraphs 6-11, the Examiner has rejected claims 34-43 under 35 U.S.C. § 112, second paragraph, as indefinite. Specifically, the Examiner objects to claim 34 for reciting concentration when maturation of dendritic cells results. The Examiner also objects to claim 34 for not reciting isolation steps of mononuclear cells possessing CD14. The Examiner also objects to the term "modified" in claim 35. The Examiner also objects to the phrase "at least one antibody" in claim 38. Finally, the Examiner objects to the terms "peptide" and "antigen" in claim 58. Applicants respectfully traverse this rejection.

Without acquiescing in the legal correctness of the rejection, but solely to bring the application closer to allowance, Applicants have amended the claims in a manner overcoming the instant rejection. Namely, Applicants have amended claim 34 to recite a process of maturing dendritic cells. Applicants have also removed the step of

isolating mononuclear cells possessing CD14. Applicants have also canceled claim 35 without prejudice or disclaimer. Applicants have also removed the term "at least one antibody" from claim 38. Applicants have also canceled claim 58 without prejudice or disclaimer. Accordingly, reconsideration and withdrawal of the rejection under § 112, second paragraph are respectfully requested.

Rejections under 35 U.S.C.§ 112, first paragraph

In paragraph 12 of the Office Action, the Examiner has rejected claims 34-43 and 57-59 under 35 U.S.C. § 112, first paragraph as lacking enablement. Specifically, the Examiner states that while the specification enables a method using fragments with 2-12 hyaluronic acid building blocks, the specification does not enable a method or vaccine wherein "dendritic cells are stimulated with 1-50 hyaluronic building blocks". Applicants respectfully traverse the rejection.

No For Vaccine

Without acquiescing in legal correctness of the rejection, but solely to bring the application closer to allowance, Applicants have amended the claims to recite that the hyaluronic acid fragments comprises from 2 to 12 building blocks. Accordingly reconsideration and withdrawal of the rejection under § 112, first paragraph are respectfully requested.

Prior Art Rejections

In paragraph 14 of the Office Action, the Examiner has rejected claims 34 and 59 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,725,585 to Wenge et al (Wenge). In paragraph 15, the Examiner has rejected claim 57 under 35 U.S.C. § 102(b) as anticipated by Noble et al (Noble). In paragraph 18, the Examiner has rejected claims 34-43 and 57-59 under 35 U.S.C. § 103(a) as obvious over Brand et al., Eur. J. Immunol. 1998. 28:1673-1680 (Brand). Applicants respectfully traverse these rejections.

Without acquiescing in the rejection, Applications have amended the claims to recite hyaluronic acid fragments that comprise from 2 to 12 building blocks, which are

about 2000-5000 Da size. Applicants respectfully submit that none of the applied references, either alone, or in any combination, teach or suggest the claimed invention.

Specifically, Wenge teaches a method that uses hyaluronic acid of 750,000 Da. Noble teaches a method that uses hyaluronic acid of 200,000 Da. However, the molecular weight of the fragments of the instant invention, i.e., of 2-12 disaccharide length are much smaller, and their size is 2000-5000 Da size. Thus, Wenge and Noble fail to anticipate the claims of the instant invention since these references fail to teach hyaluronic acid fragments that comprising from 2 to 12 building blocks.

In addition, the high-molecular weight fragments such as those described by Wenge are ineffective to stimulate dendritic cells, as shown in the attached Figure, wherein human monocyte-derived dendritic cells were cultured for 48 hours in medium with 30 μg/ml of different fragment concentrations, all prepared from endotoxin-free, high molecular weight (500-100 kDa size) hyaluronic acid (HMW-HA). The HMW-HA was sonified to generate intermediate sized hyaluronic acid fragment of 300-60 kDa size (INT-HA). Finally, low molecular weight oligosaccharides were generated by enzymatic digestion and gel column separation (2-5 kDa) (sHA). In the Figure, the numbers behind the sHA indicate the number of disaccharide units (size) of the oligosaccharides (filled bars). Dendritic cells were then stained with monoclonal antibodies directed against surface markers.

The results are shown as mean fluorescence intensities (MFI). Importantly, only sHA, including those fragments of the instant invention, induce phenotypical changes in dendritic cells that can be correlated with dendritic cell maturation. The INT-HA and HMW-HA fragments, including those fragments disclosed by the applied references did not induce phenotypical changes in dendritic cells. Applicants appreciate the opportunity to submit the attached data in a Supplemental Reply as a Declaration under 37 C.F.R. § 1.132.

In relation to the results shown in the attached Figure, the dendritic cell maturation achieved using hyaluronic acid fragments that comprise from 2 to 12 building blocks is completely unexpected in view of Wenge and Brand. In addition, these references fail to motivate one of ordinary skill to modify their disclosures to include hyaluronic acid fragments that comprise from 2 to 12 building blocks. Accordingly, Wenge and Brand fail to teach or suggest the instant invention.

In addition, Brand describes the role of extracellular matrix components of fibrinogen and type I and IV collagen not hyaluronic acid fragments. In contrast, the claims of the instant application recite hyaluronic acid fragments. Thus, Brand fails to teach or suggest the use of oligosaccahrides, much less hyaluronic acid fragments from 2 to 12 building blocks. Brand also does not motivate one of ordinary skill to modify its disclosure to include the claimed hyaluronic acid fragments.

Noble fails to remedy the deficiencies of Brand in teaching the instant invention since Noble describes a method that uses Hyaluronic acid fragments of 200,000 Da size. By contrast, the claimed low-molecular weight oligosaccharides of 2-12 disaccharide length are of 2000-5000 Da size. Further, as shown in the attached Figure, intermediate sized fragments of 300,000 - 60,000 Da size, including fragment lengths reported by Noble are ineffective to stimulate dendritic cells. Accordingly, any combination of Brand and Noble fails to teach or suggest the instant invention. Accordingly, reconsideration and withdrawal of the rejection under § 103(a) are respectfully requested.

Applicants submit that new claim 60 is patentable over the cited prior art since the applied references fail to teach or suggest process for maturing dendritic cells, comprising, *inter alia*, culturing mononuclear cells together with hyaluronic acid fragments from 2 to 12 building blocks, much less wherein the hyaluronic acid fragments are present at a concentration of 30 to 50 μg/ml. Accordingly, new claim 60 is further patentable.

Conclusion

In view of the instant amendments and remarks, reconsideration of the application and allowance of all claims is requested. If there are any issues remaining that the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the local exchange listed below.

Respectfully submitted,

Date: May 12, 2003

Patricia D. Granados
Reg. No.: 33,683

Customer No. 26633

Heller Ehrman White & McAuliffe LLP
1666 K Street, N.W., Suite 300
Washington, D.C. 20006-4004
Telephone: (202) 912-2000
Facsimile: (202) 912-2020

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34. **(Amended)** A process for **[concentrating]** **maturing** dendritic cells, comprising:

[a] isolating mononuclear cells from blood;

b) concentrating mononuclear cells possessing CD14 surface marker;

c) culturing the cells of step b) in a medium containing cytokines GM-CSF and IL-4; and

d)] culturing **mononuclear cells** **[the cells of step c)]** together with hyaluronic acid fragments**[, wherein said hyaluronic acid fragments possess from 1 to 50 hyaluronic acid basic building blocks,]** in order to cause the **mononuclear** cells to mature irreversibly into dendritic cells,

wherein said hyaluronic acid fragments comprises from 2 to 12 building blocks, and wherein said [the basic] building block **[being an aminodisaccharide consisting of] comprises** D-glucuonic acid and N-acetyl-D-glucosamine **[which are]** linked by a β1-3 glycosidic bond.

38. **(Amended)** The process of claim 34, wherein the **mononuclear** cells **[possessing] possess a [the]** CD14 surface marker **and** are concentrated using **[at least one] an** antibody that is directed against the CD14 surface marker.

39. **(Amended)** The process of claim 34, wherein the **mononuclear** cells **[possessing the] possess a** CD14 surface marker **and** are cultured in a medium that contains GM-CSF at a concentration from 5,000 to 10, 000 U/mL and IL-4 at a concentration from 100 to 1,000 U/mL.

41. **(Amended)** The process of claim 34, wherein the **mononuclear** cells **[possessing the] possess a** CD14 surface marker **and** are cultured for 72 hours to 7 days in a medium containing GM-CSF and IL-4.

42. **(Amended)** The process of claim 34, wherein the **mononuclear** cells **[in step d)]** are cultured together with hyaluronic acid fragments for at least 48 hours.

43. **(Amended)** The process of claim **[35]** **34**, wherein the hyaluronic acid fragments are chemically modified.

57. **(Amended)** A vaccine comprising dendritic cells that have been **matured by a processes according to claim 34** **[cultured with a low molecular weight hyaluronic acid fragment consisting of 1 to 50 basic units, wherein the basic unit is an aminodisaccharide consisting of D-glucuronic acid and N-acetyl-D-glucosamine linked by a β1-3 glycosidic bond]**.

Figure